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Case Series

Aripiprazole in the Treatment of Early-Onset Schizophrenia Spectrum Disorder: A Case Series in Korean Children and Adolescents

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ABSTRACT

OBJECTIVE: The aim of this case series was to assess the effectiveness and tolerability of aripiprazole in Korean children and adolescents with early-onset schizophrenia spectrum (EOSS) disorder.

METHODS: The medical records of aripiprazole-treated patients with EOSS were retrospectively reviewed. Changes in illness severity were measured using the Clinical Global Impression–Severity of Illness (CGI-S) and Clinical Global Impression–Improvement (CGI-I) scales.

RESULTS: Data from 22 children and adolescents were included (12 girls, 10 boys; mean [SD] age, 14.0 [2.4] years). The mean (SD) dosage of aripiprazole was 19.8 (9.4) mg/d (median, 18.7 mg/d; mode, 15, 30 mg/d), and the range of treatment duration was 21 to 838 days. Mean (SD) CGI-S score improved significantly from baseline to end point (from 5.7 [0.7] to 4.3 [1.4]; $P < 0.001$). Based on changes in chart-extracted CGI-I scores, significantly greater improvement was associated with negative symptoms compared with positive symptoms ($U = 25.5$; $P = 0.028$; $r = -0.47$). Aripiprazole was discontinued due to insufficient effect in 5 patients (22.7%) and treatment-emergent adverse events in 3 patients (13.6%).

CONCLUSION: The results from this small study suggest that aripiprazole was moderately effective in reducing psychotic symptoms in these Korean children and adolescents with EOSS. (*Curr Ther Res Clin Exp.* 2009;70:173–183) © 2009 Excerpta Medica Inc.

KEY WORDS: aripiprazole, early-onset schizophrenia spectrum disorder.

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INTRODUCTION

Early-onset schizophrenia spectrum (EOSS) disorder is a chronic disabling disease with poor clinical and functional outcomes.[1] Therefore, the identification of an effective and well-tolerated treatment for EOSS is essential. Mounting concerns over the tolerability of first-generation antipsychotics have encouraged the use of second-generation antipsychotics in children and adolescents with EOSS.[2] Based on results from studies in adults, the risks for weight gain and metabolic dysregulation with second-generation antipsychotics (eg, clozapine, risperidone, olanzapine, quetiapine) have become important issues.[3] Results from a retrospective study examining the US Food and Drug Administration database by comparing different age groups suggested that the risks for weight gain and hyperprolactinemia with olanzapine might be higher in children than in adults.[4,5] Because treatment with atypical antipsychotics is at times continued throughout the various stages of development in children and adolescents, we cannot rule out the possibility that adverse events that have not been reported in adult patients may exist in children.

Aripiprazole is an antipsychotic with partial agonism at several G-protein–coupled receptors (eg, D_2 and 5-HT_{1A}) and functional antagonism at several serotonin receptors (eg, 5-HT_{2A}, 5-HT_{2B}, 5-HT_6).[6] These characteristics may have resulted in decreased extrapyramidal symptom (EPS) liability and minimal prolactin elevation compared with other antipsychotics, such as risperidone.[7] The more favorable metabolic adverse-events profile of aripiprazole has been attributed to its low to moderate occupancy of histamine H_1 and α_1- and α_2-adrenergic receptors.[8] The efficacy and tolerability of aripiprazole in children and adolescents have been investigated in several open-label studies[9–13] and a randomized, double-blind, placebo-controlled study.[14] Cautious recommendations are being made about the use of aripiprazole in pediatric patients with treatment-refractory psychosis.[15]

Many questions regarding the appropriate dosage and the tolerability of aripiprazole in Asian children and adolescents remain unanswered.[16,17] Aripiprazole, which is metabolized by human cytochrome P450 (CYP) isoforms CYP3A4 and CYP2D6,[18] has been reported to have high inter- and intraindividual variability in the serum concentrations of both aripiprazole and dehydroaripiprazole, an active metabolite of aripiprazole.[19] Ethnic differences in genetic polymorphisms of CYP2D6[20] that influence the serum concentration of aripiprazole and dehydroaripiprazole have been reported.[21] Based on a literature search (MEDLINE; key terms: *ethnic, difference,* and *aripiprazole*; years: 1999–2009), no study has directly compared interethnic differences in the dosage and adverse events of aripiprazole. However, studies comparing ethnic differences in the metabolism of haloperidol[22] and risperidone,[23] which are also metabolized by CYP2D6,[24] suggest that ethnicity significantly affects the metabolism of these antipsychotics.

Randomized, double-blind, placebo-controlled studies of aripiprazole[14,25] have provided valuable information, but no method has been developed to identify the long-term effects of medication on children and adolescents through short-term controlled studies.[26] Therefore, sharing long-term clinical experiences through retrospec-

tive review of clinical practice is important in the pharmacologic treatment of children and adolescents. We report the results from a case series of clinical experience with aripiprazole in the treatment of children and adolescents with EOSS.

PATIENTS AND METHODS

Data from April 2004 (when aripiprazole was introduced) to December 2007 were collected from the inpatient and outpatient electronic health records at the Child and Adolescent Psychiatric Unit, Seoul National University Children's Hospital, Seoul, Republic of Korea. Data were included from children and adolescents aged 6 to 18 years who were diagnosed with schizophrenia or schizoaffective disorder according to the criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[27] based on a clinical interview with a parent and the child conducted by a treating psychiatrist. Diagnosis was confirmed by another board-certified child and adolescent psychiatrist (Y.K.) through review of psychiatric records from children who had been prescribed aripiprazole. The chart review and the waiver of informed consent were approved by the institutional review board at Seoul National University.

Efficacy

Chart-extracted Clinical Global Impression–Severity of Illness (CGI-S) scores were used to assess the severity of psychiatric symptoms from baseline through the end of the aripiprazole trial (scale: 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill). Clinical Global Impression–Improvement (CGI-I) scores were used to evaluate target symptom improvement at the end of the trial (1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; and 7 = very much worse).[28] Two independent board-certified psychiatrists with good inter-rater reliability ($\kappa = 0.84$) conducted the CGIs on all of the patients; the psychiatrists were blinded to each other's ratings. A third psychiatrist (Y.K.) compared the 2 ratings. If there was disagreement between the CGI ratings made by the 2 initial raters, a consensus was reached through discussion. Patients were considered to be *treatment responders* if they were assigned an end point CGI-I rating of 1 or 2.

Tolerability

Tolerability of aripiprazole was assessed retrospectively by recording adverse events based on those documented in the charts.

Statistical Analysis

Nonparametric analysis was carried out after Kolmogorov-Smirnov tests were performed to assess the normality of the data. The Wilcoxon signed rank test was performed to detect differences between baseline and end point CGI-S scores. Clinical correlates of the response and nonresponse groups were compared using the Fisher exact test for categoric data (eg, sex) and the Mann-Whitney *U* test for continuous data (eg, CGI-S ratings, medication dosage, treatment duration). The CGI-I scores of

the patients with positive target symptoms were compared with those of the patients with negative target symptoms using the Mann-Whitney *U* test. All tests were 2-tailed, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois).

RESULTS

A total of 226 children and adolescents who had been prescribed aripiprazole were identified, 22 of whom were included in the analyses and ranged in age from 6.5 to 16.8 years (12 girls, 10 boys; mean [SD] age, 14.0 [2.4] years). Seventeen patients (77.3%) were diagnosed with schizophrenia; 5 (22.7%), with schizoaffective disorder. The mean age at symptom onset was 11.8 (2.3) years. Ten patients (45.5%) reported a family history of schizophrenia or other psychotic illness. The mean dosage of aripiprazole was 19.8 (9.4) mg/d (median, 18.7 mg/d; mode, 15, 30 mg/d; 0.43 [0.18] mg/kg/d), and the mean duration of treatment was 207.9 (237.5) days (range, 21–838 days; <30 days, 7 patients; 30–<100 days, 3; 100–<200 days, 4; 200–<400 days, 5; ≥400 days, 3). A total of 21 patients (95.5%) were receiving concurrent medication (olanzapine, 7 patients; risperidone, 6; clozapine, 5; fluoxetine, 3; topiramate, 2; valproate, 2; bupropion, 1; fluvoxamine, 1; lithium, 1; methylphenidate, 1; quetiapine, 1; and venlafaxine, 1). Six patients (27.3%) were receiving multiple concomitant medications during the aripiprazole trial.

Of the 22 patients, 20 (91.0%) were treated with aripiprazole after a trial of at least 1 other atypical antipsychotic. A majority of patients (17 [77.3%]) started treatment with aripiprazole without discontinuing their prior antipsychotics to augment the insufficient effect of the prior treatment (14 [82.4%]) or because an increase in the dosage of the prior antipsychotics was not possible due to intolerable adverse events, including weight gain (4 patients [23.5%]), electroencephalographic changes (2 [11.8%]), and EPSs (1 [5.9%]).

Mean (SD) CGI-S score decreased significantly from baseline to end point (5.7 [0.7] to 4.3 [1.4]; Wilcoxon signed rank test: $t = 2.5$; $P < 0.001$; effect size = –0.54). Fifteen patients (68.2%) had scores of ≥4 (moderately ill to extremely ill) on the CGI-S at the treatment end point.

As for the assessment of target symptoms, the mean CGI-I score at study end was 2.6 (1.1) (between much improved and minimally improved). Based on CGI-I scores, 3 patients (13.6%) were considered very much improved; 10 (45.5%), much improved; 3 (13.6%), minimally improved; 5 (22.7%), no change; and 1 (4.5%), minimally worse.

A family history of schizophrenia or other psychotic disorder was significantly associated with clinical response to aripiprazole ($P = 0.027$), as was the duration of treatment ($U = 20.5$; $P = 0.009$; $r = –0.54$) (**Table**). The children diagnosed with schizophrenia were found to have a higher response rate after using aripiprazole (12/17 [70.6%]) compared with children diagnosed with schizoaffective disorder (1/5 [20.0%]). Sex, parental educational level, age at onset of symptoms, age at initiation of aripiprazole treatment, CGI-S score at baseline, and the maintenance dosage were not associated with response to aripiprazole.

Table. Baseline demographic and clinical characteristics of the study patients with early-onset schizophrenia spectrum disorder classified as nonresponders and responders based on the Clinical Global Impression–Improvement scale (N = 22).

Characteristic	Responders (n = 13)	Nonresponders (n = 9)	Test of Significance
Sex, no. (%)			Fisher exact test, $P = 0.099$
Male	8 (38.5)	2 (77.8)	
Female	5 (61.5)	7 (22.2)	
Age at initiation of aripiprazole, y			$U = 45.5$; $P = 0.38$; $r = –0.19$
Mean (SD)	14.4 (1.8)	13.4 (3.1)	
Range	10.7–16.8	6.5–16.7	
Age at onset of symptoms, y			$U = 45.5$; $P = 0.38$; $r = –0.19$
Mean (SD)	12.2 (1.9)	11.1 (2.8)	
Range	9–15	5–14	
Parental education, mean (SD), y	15.2 (2.9)	14.6 (2.9)	$U = 50.5$; $P = 0.57$; $r = –0.12$
No. (%) of patients with family history of psychotic disorders	3 (13.6)	7 (31.8)	Fisher exact test, $P = 0.027$
Diagnosis, no. (%)			Fisher exact test, $P = 0.067$
Schizophrenia	12 (92.3)	5 (55.6)	
Schizoaffective disorder	1 (7.7)	4 (44.4)	
Baseline CGI-S score*	5.6 (0.8)	5.9 (0.6)	$U = 47.5$; $P = 0.40$; $r = –0.18$
Duration of aripiprazole treatment, d			$U = 20$; $P = 0.009$; $r = –0.54$
Mean (SD)	272.8 (249.6)	114.2 (194.6)	
Range	28–838	21–596	
Aripiprazole dosage, mean (SD), mg/d	19.4 (10.7)	20.3 (7.8)	$U = 54.0$; $P = 0.761$; $r = –0.06$

CGI-S = Clinical Global Impression–Severity of Illness.
*Scale: 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill.

Eighteen patients (81.8%) had target symptoms that were classified as positive (formal thought disorder, bizarre behavior, hallucination, and delusion) and 9 (40.9%) had symptoms classified as negative (anhedonia-asociality, avolition-apathy, affective flattening, and alogia). A significantly greater improvement was found in clinical response to aripiprazole in the negative symptoms than the positive symptoms ($U = 25.5$; $P = 0.028$; $r = –0.47$). The negative symptoms were found to have a more favorable response (7/8 [87.5%]) than the positive symptoms (6/14 [42.9%]) ($P = 0.04$) (**Figure**).

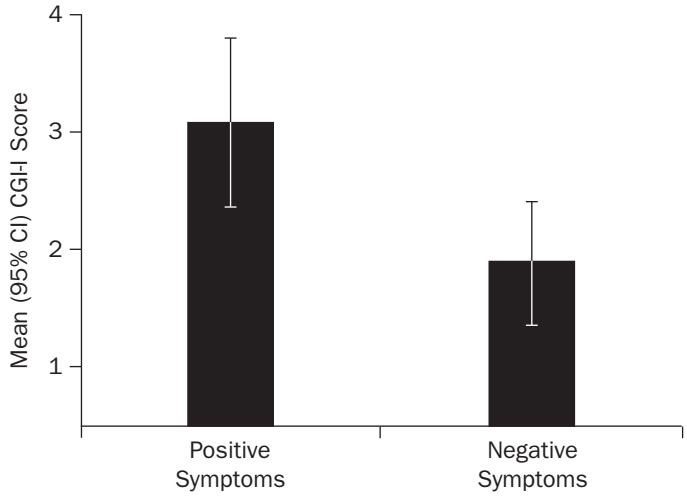

Figure. The symptom-specific clinical response to aripiprazole in 22 children and adolescents with early-onset schizophrenia spectrum disorder assessed using the Clinical Global Impression–Improvement (CGI-I) scale. The negative symptoms (7 responders and 1 nonresponder; 87.5% response) were more likely to respond to aripiprazole than the positive symptoms (6 responders and 8 nonresponders; 42.9% response). There was a statistically significant difference in the CGI-I mean scores of positive and negative symptoms to aripiprazole (U = 25.5; P = 0.028; r = –0.47).

Fourteen of the 22 patients (63.6%) were receiving aripiprazole treatment at the time of data collection. Aripiprazole treatment was discontinued due to insufficient effect in 5 patients (22.7%) and treatment-emergent adverse effects in 3 patients (13.6%) (akathisia [2] and motor EPSs [1]). The mean (SD) duration of aripiprazole use until discontinuation due to adverse events was 103.3 (84.6) days. The adverse events reported by the patients included motor EPSs (6 [27.3%] patients), insomnia (4 [18.2%]), akathisia (2 [9.1%]), nausea (2 [9.1%]), sedation (2 [9.1%]), tics (2 [9.1%]), blurred vision (1 [4.5%]), constipation (1 [4.5%]), dizziness (1 [4.5%]), and dry mouth (1 [4.5%]).

There were no significant differences between the patients who experienced adverse events and those who did not in terms of age at initiation of aripiprazole treatment (14.0 [2.8] vs 13.9 [2.0] years), age at onset of symptoms (11.8 [2.7] vs 11.8 [1.8] years), mean aripiprazole dosage (22.5 [10.1] vs 15.0 [5.8] mg/d), or duration of aripiprazole use (242.2 [276.5] vs 147.5 [143.7] days).

The weight and body mass index (BMI) at baseline and during aripiprazole treatment were available in 17 and 11 children, respectively. At the onset of aripiprazole treatment, the mean (SD) weight was 55.5 (15.1) kg (median, 56.5 kg [range, 28–85 kg]) and the mean (SD) BMI was 21.4 (3.3) kg/m^2 (median, 21.8 kg/m^2 [range, 16.1–27.4 kg/m^2]). Mean weight and BMI at the last point of data collection were 57.5 (15.4) kg (median, 58.9 kg [range, 28–83 kg]) and 21.5 (3.3) kg/m^2 (median, 22.0 kg/m^2 [range, 16.4–25.6 kg/m^2]). An increase in mean weight of 2 kg was ob-

served, but the difference was not statistically significant. The difference in mean BMI before and after aripiprazole treatment was not statistically significant.

The blood glucose and serum cholesterol concentrations at baseline and during aripiprazole treatment were available in 10 and 12 children, respectively. The mean (SD) blood glucose concentrations at baseline and at the last data collection were 93.4 (13.6) mg/dL (median, 91 mg/dL [range, 79–127 mg/dL]) and 85 (4.9) mg/dL (median, 85 mg/dL [range, 78–92 mg/dL]), respectively. Serum cholesterol concentrations were 174 (25.5) mg/dL (median, 174.5 mg/dL [range, 128–211 mg/dL]) and 167.4 (40.3) mg/dL (median, 160 mg/dL [range, 124–246 mg/dL]), respectively. Decreases in concentrations of blood glucose and cholesterol were 8.4 and 6.6 mg/dL, respectively; neither decrease was statistically significant. No significant correlations with age at the initiation of aripiprazole treatment, age at onset of illness, aripiprazole dose by weight, duration of aripiprazole treatment, or metabolic changes (weight, BMI, blood glucose concentration, and serum cholesterol concentration) were observed.

DISCUSSION

The results from the present case series suggested that aripiprazole may be moderately effective for the treatment of EOSS in children and adolescents. Results from symptom-specific assessment of treatment response using the CGI-I suggested that aripiprazole might be more effective in reducing negative symptoms. A multicenter, randomized controlled trial of aripiprazole in adolescents with schizophrenia consisting of 3 treatment groups (10 and 30 mg and placebo) reported a statistically significant reduction in Positive and Negative Syndrome Scale[29] total score compared with placebo.[14] Results from a case series of 3 adults with schizophrenia suggested that augmenting clozapine treatment with aripiprazole was effective for negative symptoms.[30] However, the results must be interpreted carefully, and future blinded controlled trials are needed to validate the findings from the present study.

Twenty-one patients (95.5%) in the present study were receiving concurrent medications, and 6 patients (27.3%) were receiving ≥2 concurrent medications during the aripiprazole trial. The high percentage of patients receiving combination therapy in the present study might mean that these cases were refractory to treatment. One retrospective chart review of studies in 248 patients reported that 82% of 28 children prescribed second-generation antipsychotics and 100% of 12 children prescribed first-generation antipsychotics were receiving multiple medications,[16] suggesting that the degree of polypharmacy was much higher in patients prescribed antipsychotics than in those prescribed other classes of psychotropic drugs. However, because the effectiveness and tolerability of polypharmacy have yet to be investigated thoroughly, careful monitoring of these patients and future research on the development of comprehensive clinical guidelines for the use of combination therapy are needed.[31]

At the time of data collection, 14 of the 22 patients (63.6%) were receiving aripiprazole treatment, resulting in a withdrawal rate of 36.4%. The high withdrawal rate may be attributable to the range of dosages used in this study (7.5–40 mg/d); this range was broader and higher than that reported in previously published studies in

children and adolescents using aripiprazole (5–20 mg/d).[10,32,33] In an open-label study in 24 children and adolescents with tic disorders in the Republic of Korea, the mean dosage was 9.8 mg/d (range, 2.5–20 mg/d).[12] Results from a review of the literature on the use of antipsychotics in children suggested a lower optimal dosage in children than in adults.[3] In the present study, 5 patients discontinued aripiprazole treatment due to insufficient effect, and the mean (SD) duration of aripiprazole use until discontinuation due to adverse events was 103.3 (84.6) days, suggesting that treatment refractoriness may have contributed more to the discontinuation of aripiprazole than the adverse events that occurred with use of the drug.

Adverse events occurred in 14 patients (63.6%) and led to treatment discontinuation in 3 patients (13.6%). This finding is consistent with those from a retrospective chart review that reported that 68% of 73 children using antipsychotics experienced an adverse drug reaction and that one third discontinued the medication.[17] Results from an open-label study of the tolerability of aripiprazole in 21 children and adolescents suggested that after forced titration to dosages of 20, 25, and 30 mg/d, 19% of the patients discontinued the medication within 1 month due to drug intolerance.[9] Long-term retrospective evaluations of aripiprazole use in 17 children and 32 adolescents have also reported that approximately half of patients experienced adverse events at a dose range of 5 to 20 mg, with a 22% to 59% discontinuation rate due to adverse events.[11,33]

In a literature review by Cheng-Shannon et al,[3] the most commonly reported adverse events that occurred with aripiprazole use in children were somnolence, vomiting, and increased appetite. A randomized controlled trial of aripiprazole (10 and 30 mg and placebo) in 302 adolescents with schizophrenia reported tremor (22.8%), EPS (17.3%), and somnolence (13.4%) as the most common adverse events.[14] Motor EPS was the most common adverse event in the present study, and aripiprazole treatment was discontinued in 3 patients due to intolerable events (akathisia [2] and motor EPS [1]). Similar rates of motor EPS and akathisia were reported among the children and adolescents with tic disorder in the Republic of Korea.[12] The results from the present study suggested that the age at treatment initiation was not associated with treatment response or susceptibility to adverse events. However, the present study may have lacked power to detect differences, and larger trials are necessary to confirm these findings.

There were several limitations to this study. The retrospective nature inherently limited interpretation of the results due to uncontrolled confounders, although the findings reflect the conventional use of aripiprazole in the routine clinical setting.[2,34] The patients might have initiated aripiprazole treatment during clinical deterioration and might have improved over time regardless of the medication administered. The study may also have lacked the power to detect meaningful differences due to its small sample size. Due to the retrospective design, there was limited information on adverse events, especially metabolic findings (eg, blood glucose and serum lipid concentrations, weight changes). The duration of treatment was heterogeneous because patients who used aripiprazole for a short duration and those who used aripiprazole long-term were both included to give clinicians information on the entire scope of aripiprazole

treatment in children with EOSS. Pharmacotherapy was the main modality of treatment in most of the patients in the present study. However, the stable milieu provided by hospitalization and the supportive psychotherapy provided by the treating clinician during outpatient visits may have been therapeutic to the patients. The sample size was small due to the rarity and severity of EOSS, and the fact that children are still developing poses certain limitations on the validity of the clinical diagnoses.

CONCLUSIONS

Although the retrospective nature of this case series must be taken into account, the results suggest that aripiprazole may be an option in the treatment of EOSS in children and adolescents. The data suggest that aripiprazole may be more effective in reducing negative than positive symptoms.

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